REMARKS/ARGUMENTS

Claims 1, 3, 5-7 and 13-27[1] are pending in this application and presented for examination. Reconsideration is respectfully requested.

Applicants note that in U.S. Patent Publication 2002/0028240, which corresponds to the subject application, on page 12, Table 4, there is an error in the entry for Sucrose. The solubility should be 1 mL, in lieu of 10 mL. The 1 mL solubility value appears in the application as filed.

I. THE INVENTION

The present invention relates *inter alia*, to a timed-release compression-coated formulation. Timed-release means, for example, that after a specific lag time, the active ingredient from the pharmaceutical preparation is released (*see*, Figure 1 of the specification). In the present invention, timed-release is achieved by the specific formulation of the core tablet and outer layer. The core tablet comprises an active ingredient and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose, and an outer layer wherein the outer layer is made from at least one type of polyethylene oxide and polyethylene glycol. The outer layer does not contain a drug.

II. DOUBLE PATENTING REJECTION

The Examiner has rejected claims 1, 3, 5-7 and 13-26 under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1, 3, 5-7 and 13-26 of co-pending U.S. Patent Application No. 11/463,570 in view of U.S. Patent No. 6,235,311 (Ullah *et al.*). In response, Applicants respectfully request that the Examiner hold this rejection in abeyance until allowable subject matter is acknowledged by the Examiner. At that time, Applicants will take the necessary steps including, for example, filing a terminal disclaimer to obviate the rejection.

III. FIRST REJECTION UNDER 35 U.S.C §103(a)

The Examiner has rejected claims 1, 7, 14-17, 21, 22, 24, 25 and 27 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,277,409 ("Luber *et al.*").

The Examiner states that Luber *et al.* teach a tablet having a inner core comprising a filler and an outer layer comprising a thermoplastic coating. According to the Examiner, "a thermoplastic coating" can be mixtures of polyethylene glycol and polyethylene oxide (column 3, lines 50-55). The Examiner further states that the core of Luber *et al.* contains fillers such as sucrose, lactose and the like (column 3, lines 3-8). With regard to the percent erosion of the filler, the Examiner alleges that this would be an inherent limitation to any filler meeting the limitations of the claims. The Examiner continues to maintain that the claim is in a product-by-process format. In response, Applicants respectfully traverse the rejection.

A claim is considered obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. One of the rationales addressed by the court in *KSR* supports a finding of obviousness when the prior art reference (or combination of references) (1) teaches or suggests the claim elements; (2) provides some suggestion or motivation to combine the references; and (3) provides a reasonable expectation of success (MPEP § 2143).

[1] The Office Action Summary incorrectly recites the pending claims as "1, 3, 5-7 and 13-26."

1. The reference does not teach all the claim limitations

In the present invention, the formulation tablet comprises a core and an outer layer. The core tablet comprises the active ingredient and a freely erodible filler. The freely erodible filler is 1 or 2 or more selected from the group of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose. On the other hand, the outer layer is made from at least one type of polyethylene oxide and polyethylene glycol and does not contain a drug.

As currently claimed, the core tablet is capable of approximately 40 to approximately 90% erosion. Surprisingly, Applicants have found that a percent erosion of the core tablet of approximately 40 to approximately 90% is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability (see, page 4, lines 16-24 of the Specification). Before the advent of the present invention, the requirement for 40 to approximately 90% erosion to obtain an ideal timed-release pharmaceutical preparation was unknown.

The tablet of Luber *et al.* has nothing at all to do with a timed-release formulation. Luber *et al.* teach a hard outer coating for a soft chewable core (see, column 1, lines 45-48; column 3, lines 28-30; and Example 1, column 4, lines 36-39). Luber *et al.* teach a process for coating a tablet having a hardness of up to 15 kp/cm^2. The molten thermoplastic material acts as a protective coating for a chewable core having an active agent.

Luber *et al.* teach that the "protective coating" is prepared as follows :

> After the tablet core has been made, it is then coated with a molten composition comprising at least one thermoplastic material having a melting point of less than about 120°C. Preferably, the melting point of the thermoplastic material is less than about 100°C., more preferably less than about 80°C. Examples of suitable thermoplastic materials include fats such as cocoa butter, hydrogenated vegetable oils such as palm kernel, cottonseed oil, sunflower oil, and soybean oil, mono, di, and triglycerides, phospholipids, waxes such as Carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax, water soluble polymers such as polyethylene glycol, polyethylene oxides and derivatives, and sucrose esters. Preferably, the thermoplastic material is selected from hydrogenated vegetable oil, polyethylene glycol, waxes, and mixtures thereof. [Emphasis added, see, column 3, lines 43-56]

The protective *molten wax* and thermoplastic materials of Luber *et al.*, which make a hard outer layer (up to 15 kp/cm^2) for the tablet, are in no way similar to the present invention. The process of Luber *et al.* makes these materials much different than the present invention. In fact, the waxy coating of Luber *et al.* prevents erosion (*e.g.*, shelf-life) of the inner core. Luber *et al.* teach at column 4, lines 14-19:

> Advantageously, the protective coating provides an impact resistant and water resistant cover of the tablet core. This stabilizes the friability of the tablet, and in addition *prevents erosion* of the tablet core by any outer coatings present on the tablet, which are of a relatively hydrophilic nature. [Emphasis added].

The molten wax of Luber *et al.* teaches away from the present invention as it *prevents erosion* of the inner core. But in any event, the tablet of Luber *et al.* is designed to be chewed.

In the claimed invention, a percent erosion of the core tablet of approximately 40% to approximately 90% is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability. The molten wax of Luber *et al. prevents erosion* of the inner core and is designed to be chewed. Therefore, Applicants submit that it will not inherently have an erosion of approximately 40% to approximately 90%, which is necessary for a timed-release pharmaceutical preparation as claimed.

The Examiner takes the position that any filler of the cited art, if it meets the limitation of the claims, would act identically to erode to the given percentage as claimed. Applicants respectfully disagree.

In the present case, as the hydrophilic base of the outer layer absorbs water, a hydrogel forms in order to retain the water, and the water in the tablet penetrates into the inner layer eroding the filler (e.g., 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose) such that the inner core substantially becomes a solution state or suspension state. The result is that as the inventive tablet moves from the upper digestive tract to the lower digestive tract, the tablet has an outer layer that is slowly dissolving, but substantially retaining water, and the inner core is

substantially liquid. The advantage of having a substantially liquid inner layer is that when the outer layer is finally peeled away, the inner layer does not then have to dissolve in order to enable absorption of the drug (its already a suspension or a liquid). When the outer layer dissolves, the inner layer is already substantially dissolved and enables rapid absorption.

To address the Examiner's concern regarding percent erosion raised in paragraph 8, page 4 of the Office Action, the reason "sucrose" and "lactose" of Luber *et al.* do not inherently meet the limitations of the current claim is that Luber *et al.* teach a fundamentally different tablet architecture. The tablet of Luber *et al.* will simply not result in the percent erosion as immediately described because the molten wax and chewable tablet as described in Luber *et al.* will physically and chemically not allow it. The architecture of Luber *et al.* simply will not allow the filler to erode while still being encapsulated by the outer layer! The outer layer of Luber *et al. prevents* erosion whereas the outer layer of the current invention promotes it. In addition, as is explained more fully below, "lactose" is used in a comparative example and is not claimed as a core component.

With regard to providing evidence, Applicants respectfully direct the Examiner's attention to page 28 of the Specification as filed. As illustrated by the data therein, Example 5 (inventive), which has a higher percent erosion of the inner core prior to dissolution of the outer layer, results in better absorption of the drug compared to Comparative Example 2 (comparative). The components of the two formulations (Inventive vs Comparative) are set forth below for the convenience of the Examiner:

Example 5		**Comparative Example 2**
A. Core		A. Core
50 mg acetaminophen		50 mg acetaminophen
25 mg PEO		25 mg PEO
75 mg sucrose		75 mg lactose
B. Outer Layer		B. Outer Layer
125 mg PEO		125 mg PEO

125 mg PEG		125 mg PEG
C. AUC 1054 ng.h/ml		C. AUC 387 ng.h/ml.

The AUC for the inventive formulation is 1054 ng.h/ml, whereas the AUC for the comparative formulation is only 387 ng.h/ml. The inventive formulation has a much higher absorption. This is objective evidence which rebuts any *prima facie* case of obviousness.

In paragraph 9, on page 5 of the Office Action, the Examiner reiterates the notion that the claims are somehow product-by-process claims and then uses this mischaracterization of claims to attached law which is clearly improper. In this respect, Applicants respectfully point out to the Examiner M.P.E.P. § 2173.05(p), which describes a product-by-process claim as defining the product in terms of the process by which it is made. Contrary to the Examiner's assertion, the % erosion of the formulation is what occurs to the core of the formulation *in vivo*. The core of the formulation is eroded, peeled away or "unmade" to the claimed percent erosion. The percent erosion feature of the product is in fact the complete opposite of a "product-by-process" claim, because the "product" is being "disassembled" peeled away or "unmade" through the erosion process. The core is not being made as is required for a product-by-process claim, but the core is being unmade by erosion.

With respect to the feature of "compression-coated," this is a term of art well known to a skilled artisan. It is not a product-by-process as the "steps of process are not described" only the product after the process.

In view of the foregoing, Applicants submit that Luber *et al.* in no way renders the instant invention obvious. As such, Applicants respectfully request that the rejection of the claims be withdrawn.

IV. SECOND REJECTION UNDER 35 U.S.C §103(a)

The Examiner has rejected claims 1, 3, 5-7, and 13-26 as allegedly being obvious over the combined disclosures of Luber *et al.,* in view of Sako *et al.,* (EP 0 661 045) and Taniguchi *et al.,* (EP 0 709 386). In response, Applicants respectfully traverse the rejection.

In combining the references, *KSR* dictates that there must be some nexus between the references in order for the combination to be proper. In the present combination of references, there is no rational underpinning to support a legal conclusion of obviousness. (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). The Examiner has acknowledged the deficiencies of Luber *et al.* in paragraph 13, on Page 6 of the Office Action dated February 20, 2008. However, in paragraph 14, page 7, in the last two lines of the Office Action, the Examiner states:

> The reference establishes the level of skill in the art regarding specific fillers and their relationship to compression coatings and hydrogel-forming compression tablets. The artisan of ordinary skill would have been able to include the fillers of the **'045 reference into the '409 since both formulation disclose similar formulations**. [Emphasis added].

Applicants strenuously and fundamentally disagree with the Examiner's characterization of the formulations disclosed in these two references. Under *KSR*, there must be some underpinning between Luber *et al.* and Sako *et al.* in order to combine their teachings. However, there is absolutely no rational similarity between Luber *et al.* and Sako *et al.* In contrast to the chewable dual-layered tablet with the *molten wax* outer layer of Luber *et al.,* Sako *et al.* teach a *sustained-release tablet* (not timed-release as claimed) in a single-layered formulation. Sako *et al.* teach a tablet that contains a *single-layer*, *i.e.*, a homogeneous formulation which comprises a i) a drug, ii) an additive providing for the penetration of water in to the core of the preparation, and iii) a hydrogel-forming polymer. The tablet travels through the digestive system and the tablet is continuously eroded, thereby releasing drug at every step along the way, from the upper digestive tract to the colon.

The architecture of the formulation disclosed in Luber *et al.* and its mode of action is on the opposite end of the spectrum compared to the formulation disclosed and taught in

Sako *et al.* The two tablets are completely different. Contrary to the Examiner's assertion, there exists no rational similarity between these references.

Moreover, the teaching of Sako *et al.* is much different than the current invention. Sako *et al.* do not teach or suggest an erodible core and outer layer as claimed. The core tablet in the inventive formulation *does not* contain a hydrogel polymer. This is in clear contrast to the disclosure of Sako *et al.*, which is a homogenous sustained release tablet comprising i) an active agent; ii) an additive, *e.g.*, a hydrophilic base; *and iii) a hydrogel forming polymer.*

Taniguchi *et al.* teach benzazepeine compounds and pharmaceutical compositions thereof. Taniguchi *et al.* disclose a list of general pharmaceutical ingredients that can used to formulate a tablet composition comprising the benzazepeine compounds (*see*, page 27, lines 30-37).

Luber *et al.*, Sako *et al.*, and Taniguchi *et al.*, alone or when combined, simply do not teach or suggest the specific combination of a core comprising the freely erodible filler for a drug that is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid, polyethylene glycol, sucrose, and lactulose, and the outer layer that is made from at least one type of polyethylene oxide, and polyethylene glycol. The combination of references do not teach the all the features of the claims.

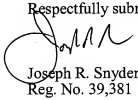
Moreover, there is simply no rational underpinning between the references. Thus, a skilled artisan would not combine their teachings. In view of the combination of references, the present invention is not rendered obvious. Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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